Relationship between maternal pregnancy-related anxiety and þÿinfant brain responses to emotional speech a p

Maria, Ambika

2020-02-01

Maria , A , Nissilä , I , Shekhar , S , Kotilahti , K , Tuulari , J J , Hirvi , P , Huotilainen , M , Heiskala , J , Karlsson , L & Karlsson , H 2020 , ' Relationship between maternal þÿpregnancy-related anxiety and infant brain responses to emotional spe Journal of Affective Disorders , vol. 262 , pp. 62-70 . https://doi.org/10.1016/j.jad.2019.10.047

http://hdl.handle.net/10138/309867
https://doi.org/10.1016/j.jad.2019.10.047

Journal of Affective Disorders 262 (2020) 62–70

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Relationship between maternal pregnancy-related anxiety and infant brain responses to emotional speech – a pilot study

Ambika Maria[a], Ilkka Nissilä[b,*], Shashank Shekhar[a,c], Kalle Kotilahti[b], Jetro J. Tuulari[a,d,e,f], Pauliina Hirvi[b,g], Minna Huotilainen[a,h], Juha Heiskala[i], Linnea Karlsson[a,j], Hasse Karlsson[a,f]

[a] University of Turku, Institute of Clinical Medicine, Turku Brain and Mind Center, FinnBrain Birth Cohort Study, Turku, Finland
[b] Aalto University, Department of Neuroscience and Biomedical Engineering, Finland
[c] University of Mississippi Medical Center, Department of Neurology, MS, USA
[d] The Turku Collegium for Science and Medicine (TCSM)
[e] University of Oxford, Department of Psychiatry, Oxford, United Kingdom
[f] University of Turku and Turku University Hospital, Department of Psychiatry, Turku, Finland
[g] Aalto University, Department of Mathematics and Systems Analysis, Finland
[h] University of Helsinki, Faculty of Educational Sciences, CICERO Learning, Finland
[i] Helsinki University Central Hospital, Department of Clinical Neurophysiology, Finland
[j] University of Turku and Turku University Hospital, Department of Child Psychiatry, Turku, Finland

ARTICLE INFO

Keywords:
Maternal anxiety
Pregnancy
Infant
Emotion
Speech
Diffuse optical tomography

ABSTRACT

Background: Maternal pregnancy-related anxiety (PRA) is reportedly related to neurodevelopmental outcomes of infants. However, the relationship between maternal PRA and the processing of emotions in the infant brain has not been extensively studied with neuroimaging. The objective of the present pilot study is to investigate the relationship between maternal PRA and infant hemodynamic responses to emotional speech at two months of age.

Methods: The study sample included 19 mother-infant dyads from a general sample of a population of Caucasian mothers. Self-reported Pregnancy-Related Anxiety Questionnaire (PRAQ-R2) data was collected from mothers during pregnancy at gestational weeks (gwks) 24 (N = 19) and 34 (N = 18). When their infants were two months old, the infants' brains functional responses to emotional speech in the left fronto-temporoparietal cortex were recorded using diffuse optical tomography (DOT).

Results: Maternal PRAQ-R2 scores at gwk 24 correlated negatively with the total hemoglobin (HbT) responses to sad speech on both sides of the temporoparietal junction (Spearman's rank correlation coefficient ρ = -0.87). The correlation was significantly greater at gwk 24 than gwk 34 (ρ = -0.42).

Limitations: The field of view of the measurement did not include the right hemisphere or parts of the frontal cortex. The sample size is moderate and the mothers were relatively highly educated, thus there may be some differences between the study sample and the general population.

Conclusions: Maternal pregnancy-related anxiety may affect child brain emotion processing development. Further research is needed to understand the functional and developmental significance of the findings.

1. Introduction

Recent behavioral (e.g., neuropsychological) and physiological (e.g., event-related potential (ERP) and functional magnetic resonance imaging (fMRI)) studies indicate that maternal anxiety during pregnancy is related to neurodevelopmental changes in the offspring (Schetter and Tanner, 2012), including impulsivity (Van den Bergh et al., 2005a), alterations in auditory attention (Harvinson et al., 2009; Hunter et al., 2012; Otte et al., 2015; Van den Heuvel et al., 2015) and cognitive control (Mennes et al., 2006, 2009; Van den Bergh et al., 2005a). Moreover, maternal anxiety symptoms during pregnancy have been associated with behavioral/emotional problems in children (Martin et al., 1999; O'Connor et al., 2002a, 2002b, 2003; Van den Bergh et al., 2004; Wachs et al., 2009; Goodman et al., 2011; Herba et al., 2016). Different from general anxiety, pregnancy-related anxiety (or pregnancy-specific anxiety) refers to worries specifically

* **Corresponding author at:** Department of Neuroscience and Biomedical Engineering, Aalto University, Aalto University School of Science, P.O. Box 12200, FI-00076 AALTO, Espoo, Finland.
E-mail address: ilkka.nissila@aalto.fi (I. Nissilä).

https://doi.org/10.1016/j.jad.2019.10.047
Received 10 May 2019; Received in revised form 9 September 2019; Accepted 28 October 2019
Available online 30 October 2019

concerning the pregnancy, changes in appearance, labor and birth, the health of the developing child and future parenting (Huizink et al., 2004; Blackmore et al., 2016). Albeit not representing any maternal medical condition as the actual anxiety disorders, maternal pregnancy-related anxiety has been consistently linked with child neurodevelopmental outcomes, such as cognitive development, anxiety and brain morphology (Buss et al., 2010, 2011; Davis and Sandman, 2010, 2012; Huizink et al., 2003; Nolvi et al., 2016; Korja et al., 2017).

An important domain of neurodevelopment in humans is the processing of emotional stimuli and signals. Emotional messages are carried, for example, by vocal expressions along with the meaning of the words, and these messages are crucial for social communication in humans, likely important for survival and social cohesion (Scherer, 1986, 1995; Bachorowski, 1999). Acoustic cues are helpful in conveying the intended emotion by the speaker while the perception of these cues helps in the inference of the expressed emotion (Johar, 2015). Emotion-specific patterns of acoustic cues can be used to communicate discrete emotions in vocal expression (Juslin and Laukka, 2003). Furthermore, the ability to decode basic emotions (fear, anger, happiness, sadness, and love) from vocal expression seems to develop already in infancy as identified by neuroimaging studies (Juslin and Laukka, 2003; Grossmann et al., 2010; Blasi et al., 2011).

In infants, the processing of auditory stimuli has been previously studied using near-infrared spectroscopy (NIRS), which is a safe, quiet and non-invasive neuroimaging tool (Kotilahti et al., 2005; Telkemeyer et al., 2009; Armitisu et al., 2011; Zhang et al., 2017; Maria et al., 2018). High-density diffuse optical tomography (DOT) is a three-dimensional (3D) imaging method with better spatial and quantitative accuracy than the basic NIRS technique (Zeff et al., 2007; Heiskala et al., 2009; Näsi et al., 2013; Lee et al., 2017, Jönsson et al., 2018; Shekhar et al., 2019). Previous NIRS studies have demonstrated that the left frontal and temporal areas are activated in infants while processing infant-directed speech (IDS) (Peña et al., 2003; Saito et al., 2009; Kotilahti et al., 2010; Naoi et al., 2012). Additionally, bilateral activation of these areas has been observed in response to IDS (Saito et al., 2007; Naoi et al., 2013).

In particular, emotional speech prosodies (suprasegmental characteristics of speech like intonation, rhythm and stress) have also been investigated using NIRS in children. Zhang et al. reported greater activation in the right temporal cortex (mainly the middle temporal gyrus and superior temporal gyrus) to emotional compared to neutral prosody in neonates as early as 2–8 days of age. Furthermore, a right parietal area (approximately located in the supramarginal gyrus) was noted to show a heightened sensitivity to fearful relative to happy and neutral prosodies (Zhang et al., 2017). Grossmann et al. (2010) observed that hearing words with emotional prosody (happy and angry), but not neutral prosody, caused activation in the right temporal cortex in 7-month-old infants. Besides, hearing angry prosody caused more activation in the right temporal cortex than happy prosody. Happy prosody (but not angry or neutral) caused activation in the right inferior frontal cortex of 7-month-old infants, which implies the engagement of frontal lobes in the evaluation of happy speech (Grossmann et al., 2010). Shekhar et al. reported greater activation to happy than neutral speech in temporoparietal regions of the left hemisphere (LHS) of two-month-old-infants using DOT, illustrating that also the LHS is involved in the processing of emotion in speech stimuli (Shekhar et al., 2019). Blasi et al. reported differential blood oxygenation level dependent (BOLD) responses to sad vs. neutral vocalizations in areas of the LHS (Blasi et al., 2011).

Recent neuroimaging studies have begun to explore the relationship between prenatal exposures, such as maternal stress on infant brain function and development. Using fMRI, Graham et al. found that maternal reports of inter-parental conflict were positively correlated with 6- to 12-month-old infants' blood oxygen-level dependent (BOLD) responses to angry speech relative to neutral speech in several brain areas (rostral anterior cingulate cortex and subcortical areas including the hypothalamus) involved in emotion and stress reactivity and regulation (Graham et al., 2013). An ERP study by Van den Heuvel et al. reported that maternal general anxiety at the beginning of the second trimester of pregnancy affects infant brain responses to sounds at 9 months of age (Van den Heuvel et al., 2014). A review by Van den Bergh et al. highlighted that maternal prenatal stress experienced during different time periods of gestation seems to be linked with infant neurodevelopmental outcomes, such as changes in cerebral processing and in structural and functional brain connectivity involving the amygdalae and prefrontal cortex (Van den Bergh et al., 2017).

However, there are no reported studies on whether pregnancy-specific anxiety experienced by mothers during pregnancy is related to infant brain responses to different emotions in speech. Therefore, in this exploratory study, we wanted to investigate the effects of maternal self-reported pregnancy-related anxiety on two-month-old infants' neural responses to emotional speech. We used DOT to measure the total hemoglobin (HbT) responses to happy, neutral, angry and sad speech in the infant's frontal, temporal and parietal areas of the left hemisphere and correlated the responses with the maternal prenatal pregnancy-related anxiety questionnaire data collected during gestational weeks (gwks) 24 and 34 of the pregnancy. As highlighted above, recent studies have shown that maternal pregnancy-related anxiety is associated with altered neurocognitive outcomes of the infants, we hypothesized that maternal pregnancy-related anxiety is related to the patterns of infant processing of emotional speech.

2. Methods

The Ethics Committee of the University of Turku approved the study protocol, and the study was conducted according to the Declaration of Helsinki.

2.1. Recruitment and selection of study participants

The study sample consisted of Caucasian mother-infant dyads recruited randomly from the FinnBrain Birth Cohort Study, from the families in which the children were born between June 2012 and October 2014 (Karlsson et al., 2018). Informed written consent was obtained from the parents on behalf of the infants before the measurement. All families were Finnish-speaking. Exclusion criteria included prenatal cigarette smoking, preterm birth, major physical disabilities and birth complications.

Measurements using DOT were attempted on 46 infants, however, because of the subject restlessness (25) and missing questionnaire data (2), only the high-quality data from 19 subjects were used in this study. To be included, minimum requirements for data quality were set so that at least four artifact-free time courses for the responses to each of the four emotional speech stimulus conditions (happy, angry, sad and neutral) were acquired.

2.2. Questionnaire data

Pregnancy-Related Anxiety Questionnaire-Revised (PRAQ-R2) was used as a measure of pregnancy-related anxiety (Huizink et al., 2016). This self-reported questionnaire data was gathered with postal/electronic questionnaires at two time points during pregnancy at gwks 24 and 34 (Karlsson et al., 2018). PRAQ-R2 is a questionnaire based on PRAQ and it was revised to be applicable for pregnant women regardless of parity. It consists of ten items rated from 1 to 5 and measures the same constructs repeatedly during pregnancy (Huizink et al., 2016). The questions reflect concern about one's own appearance, fear of giving birth and worries about the physical or mental health of the baby. The mothers had to choose from options 1 to 5 (1 = Absolutely not relevant, 2 = Hardly ever relevant, 3 = Sometimes relevant, 4 = Reasonably relevant and 5 = Very relevant). Higher PRAQ-R2 values indicate higher levels of pregnancy-related anxiety. PRAQ-R2

appears to be a strong predictor of birth-related and childhood outcomes, independent of general anxiety measures (Huizink et al., 2002, 2003, 2016; Reck et al., 2013). The mean maternal PRAQ-R2 scores corresponding to the successfully measured and rejected dyads were compared statistically in the Supplement.

2.3. Instrumentation

A 16-channel DOT system developed at Aalto University was used in this study (Nissilä et al., 2002; Nissilä et al., 2005). We report only HbT in the present study, as changes in HbT have been reported to be more specific to arteriolar and capillary areas and therefore more accurately reflect the site of neuronal activity than oxygenated (HbO_2) and deoxygenated hemoglobin (HbR), which include significant contributions from venous drain areas (Culver et al., 2005; Hillman et al., 2007).

2.4. Measurement session

The measurements were carried out in a room with dimmed ambient lighting. During the session, the mother was sitting in a comfortable chair and the infant was lying on the mother's lap. Before and during the neuroimaging session, the infant was fed by the mother, if needed, to help them stay calm during the measurement. Photogrammetry markers were placed on the infant's head and images were taken from five to seven different directions using a stereo camera setup. Fig. 1a illustrates the measurement setup.

We used a silicone (Accutrans, Ultronics/Coltène) based high-density fiberoptic probe with 15 source fibers and 15 detector fiber bundles. The probe was placed over the left fronto-temporal cortex of the infants using a self-adhesive bandage (Fig. 1b). The approximate field of view (FOV) of the probe is illustrated using contour lines that represent the falloff of measurement sensitivity in Fig. 1c and d. The FOV is defined as the region where the measurement sensitivity for at least one source-detector pair is greater than 1/1000th of the maximum value of the sensitivity for each of the 19 subjects (dark gray contour line in Fig. 1c and d). We decided to limit the measurement to one hemisphere to make it easier for the mother to support and take care of the infant during the recording. The left hemisphere was selected based on our previous studies (Kotilahti et al., 2010) and the findings in Blasi et al. (2011). After the probe was attached, additional stereo images were taken to record the probe position relative to the external landmarks. The entire measurement session was video recorded to assist in the detection of motion artifacts. If the infant was crying or uncomfortable, the measurement was paused to console the infant. If the infant continued to be uncomfortable, or the mother asked for the measurement to stop, the session was terminated.

2.5. Stimuli

The stimuli consisted of 11-s trains of four short phrases spoken in a happy, angry, sad or neutral tone of voice. These phrases were spoken in Finnish by an actress and were presented using a computer running Presentation (Neurobehavioral Systems©) software and a loudspeaker. The stimuli had different words and short pharases with appropriate semantic content fitting to each emotion. Each block contained stimulation from only one emotional category. The silent rest period was randomized in duration from 20 s to 30 s between each stimulation block. The loudspeaker was placed at approximately two meters from the infant. The sound intensity was set to approximately 65 dB. One to three runs of 25 min duration were measured for each infant.

2.6. Signal processing

The modulation amplitude was the data type used in this study. The amplitude signal was band-pass filtered with −3 dB cutoff frequencies of 0.007 Hz and 0.2 Hz. Motion artifacts were identified by thresholding the filtered amplitude signal at a manually selected threshold from 3.5 to 7 times the standard deviation of the signal, and stimulus triggers inside or near epochs with suprathreshold filtered amplitude values were removed to avoid the impact of motion artifacts on the calculated average. The threshold was selected by visual inspection of the signal. Vigorous limb movement or head movement identified from the video were also used to reject the affected responses. Out of the 46 subjects measured, data from 25 were considered insufficient quantity and quality to be used, and questionnaire data from two of the remaining subjects were not available for gwk 24 (three for gwk 34). The analysis was based on the remaining 19 subjects (8 females and 11 males) for PRAQ-R2 gwk 24 and for 18 subjects (7 females and 11 males) for gwk 34. The successful measurements included PRAQ-R2 values across a broad range (10–45). After removal of motion artifacts, 8 ± 2 (mean ± SD) presentations of each stimulus type remained for averaging, which was performed using deconvolution. Prior to reconstruction, the mean value in the interval [−1 s, 0 s] was subtracted from the averaged time courses for each source-detector pair.

2.7. Anatomical model

A representative 1.5-month-old infant's magnetic resonance image (MRI) was segmented into tissue types (see Jönsson et al., 2018 for the optical properties assigned to each tissue type) and photogrammetry marker coordinates were used to scale the model for each child (see Section 2.8). The resulting voxel-based anatomical model was used in the calculation of the Jacobians and the reconstructed images as well as to visualize the location of the clusters found (Fig. 2).

2.8. Photogrammetry

Five to seven pairs of stereo images were captured from different orientations while the infant was wearing a colored glass pearl marker mesh and additional markers on the face and at landmarks (left and right pre-auricular points and the nasion). The 3D positions of the landmarks from the photogrammetry were used to co-register the optode positions on the surface of the scalp of the voxel-based anatomical model. The voxel side length of the anatomical model was adjusted to minimize the squared radial distance between photogrammetry markers and the outer surface of the scalp in the anatomical model.

2.9. Image reconstruction

A linear approximation for the dependency between changes in the logarithm of amplitude and absorption coefficient was used to reconstruct the changes in the absorption coefficient. The Jacobian matrices were calculated from Monte Carlo simulations using the Monte Carlo eXtreme (MCX) open source software (Fang et al., 2009) on a NVIDIA Tesla K80 graphics processing unit (GPU)-card. We simulated 10^9 photon packets for 9×10^{-8} s per source using source and detector radii of 1.25 mm and 1.82 mm, respectively. Voxel-wise absorption coefficient changes were reconstructed as the least-squares solution to the difference between measured and estimated difference data including Tikhonov regularization with the Laplacian matrix (Heiskala et al., 2009; Näsi et al., 2013). Only data from source-detector pairs with separation under 45 mm was used (Fig. 1e). The performance of the reconstruction algorithm was validated via simulations and phantom experiments. The absorption coefficient changes were converted to HbT changes using the extinction coefficients from Cope (1991).

2.10. Voxel-based clustering analysis

To search for the regions that exhibited a statistically significant correlation between the HbT responses to emotional speech and the maternal pregnancy-related anxiety scores, we calculated Spearman's

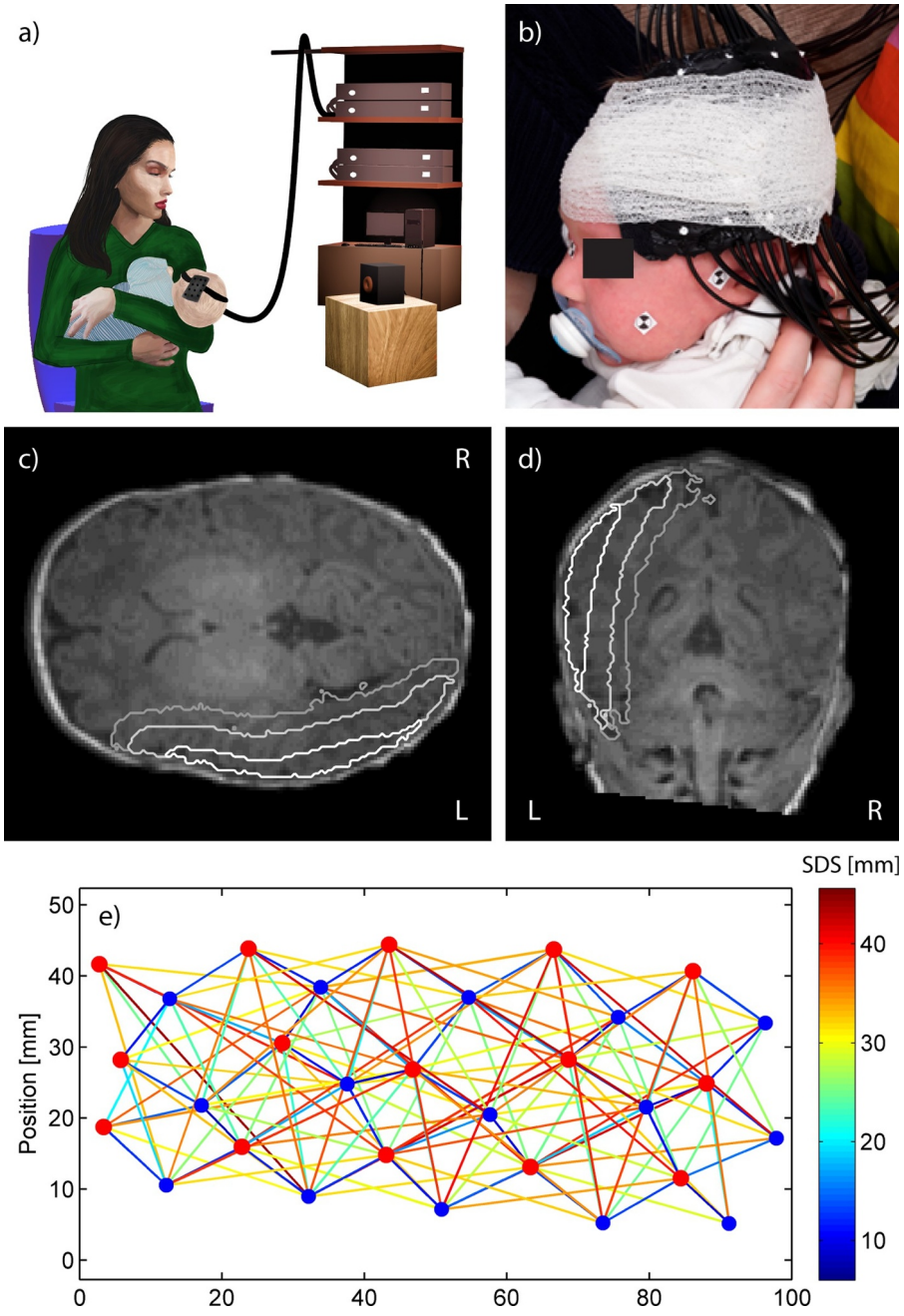

Fig. 1. Illustration of a) the measurement session, b) the position of the probe, c) the axial and d) coronal views of the approximate field-of-view, and e) the source (red dot) and detector (blue dot) arrangement with active pairs marked with interconnecting lines. The measurement sensitivity is indicated using the white, light gray and dark gray contour lines (in c-d) representing thresholds where the sensitivity exceeds 1/10th, 1/100th, and 1/1000th of the maximum value of the Jacobian for all subjects.

rank correlation coefficient and the corresponding p-value for each voxel within the field of view (FOV) of the measurement probe for each pair of stimulus condition and maternal distress score. Spearman's rank correlation was used because the relationship may be nonlinear. The HbT response magnitude was calculated by averaging the time course from 2 s to 18 s post stimulus train onset. Adjacent gray matter (GM) voxels with $p < 0.001$ were combined into clusters and the voxel response values within the cluster were averaged. After this, the cluster was expanded to include adjacent voxels with $p < 0.0033$ and finally $p < 0.01$. Finally, cluster-level correlation coefficients and cluster-level p-values were calculated for each of the voxel-level p-value thresholds and the extent of the cluster was decided based on the lowest cluster-wise p-value. Multiple comparison correction using the Bonferroni method was applied to the cluster p-value based on the following considerations: The GM volume within the FOV of measurement was approximately 101 cm^3. Our imaging method is considered to be able to distinguish between regions of 1 cm^3 in volume, which leads to a correction factor of 101. The number of source-detector pairs with source-detector separation (SDS) > 12 mm was 120, leading to our selection of the correction factor as 120. A second, more stringent correction factor was calculated by considering also the number of conditions (4) and the number of questionnaire pregnancy time points (2), leading to a factor of $120 \times 4 \times 2 = 960$. A validation procedure was applied to determine the dependency of the false positive rate on the minimum cluster size threshold in the following way: A large quantity of synthetic resting state data that matches the spatiotemporal cross-correlation

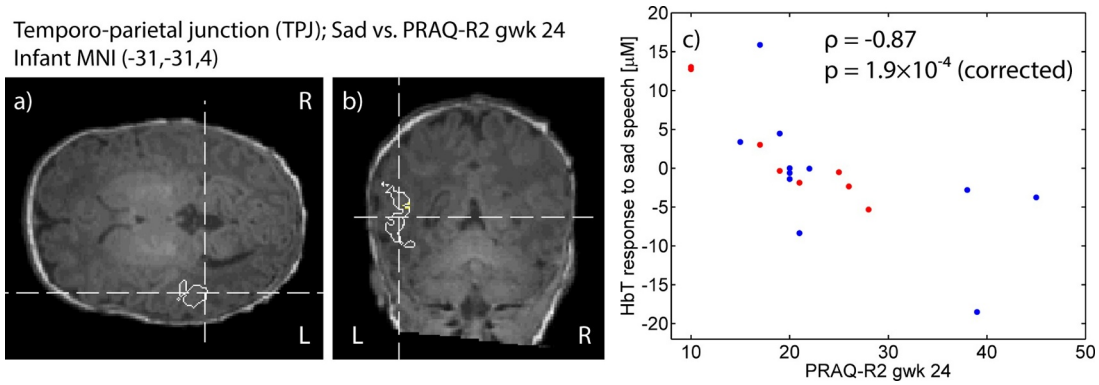

Fig. 2. Temporoparietal junction (TPJ) cluster with statistically significant negative correlation between infant response to sad speech and pregnancy-related anxiety (PRAQ-R2) at gwk 24. Cluster location (a) in the axial slice through the center of gravity, (b) coronal slice. White line shows cluster outline for voxel-level $p < 0.01$ and solid yellow area corresponds to voxel-level $p < 0.001$. c) Scatter plot showing the individual subject HbT responses to sad speech and the infant's mothers' PRAQ-R2 scores for gwk 24.

structure of measured infant resting state data was generated using autoregressive modeling. The analysis pipeline was applied to the synthetic resting state data generated and the number of clusters that were classified as statistically significant was counted along with the cluster size. A false positive rate of 0.05 was achieved when the minimum cluster size was set to 674 voxels.

2.11. Identification of anatomical regions

Using visual inspection, the anatomical regions corresponding to the clusters were identified using the anatomical images and automatic anatomical labeling (AAL) maps of the newborn atlas published by Shi et al. (2011). The approximate infant and adult Montreal Neurological Institute (MNI) coordinates corresponding to the centers of gravity of each cluster were determined using the Shi and MNI atlases with MRIcron and are shown in Table 2.

2.12. Analysis of the contribution of potentially confounding factors

On the cluster found to have a statistically significant Spearman's rank correlation coefficient between PRAQ-R2 and HbT response to the emotional speech, we performed a linear regression analysis to evaluate possible confounding effects of PRAQ-R2 with maternal prenatal depression and general anxiety symptoms. Maternal postnatal depression and general anxiety recorded at 3 months after birth were also tested as potential confounders. Finally, we tested the gestational age at birth as a possible confound due to the rapid anatomical functional changes that occur towards the end of pregnancy. This analysis is presented in the Supplement.

3. Results

3.1. Characteristics of the successfully measured dyads

Table 1 shows descriptive statistics of the 19 mother-infant dyads that were included in the analysis of our study. The participant mothers had a median age of 32.1 (range 21.4 – 37.3) years at the time of the DOT measurement of their infants. The mothers' education was characterized using a three-step scale (1 = lower or middle level education (up to 12 years of education), 2 = vocational/applied university degree (up to 15 years of education), 3 = university degree (more than 15 years of education)). The mothers had an average monthly income of 2000 to 2500 euros, which could be considered as middle-class income in Finland (Statistics Finland 2017). The study sample was generally highly educated: 58% of the mothers had a university degree and the symptom levels were generally low. None of the mothers in the study sample reported smoking during pregnancy. None of the mothers were under antidepressant or antipsychotic medication during pregnancy. The age of the participant infants (8 females and 11 males) ranged from 6 weeks to 10 weeks (mean 55 ± 9 days standard deviation (SD)). Additional information on the participants is included in the Supplement.

3.2. Statistically significant clusters

A cluster (1928 voxels; approximate infant MNI coordinates $x = -31$, $y = -31$ and $z = 4$; Fig. 2a and b) in the left temporoparietal junction (TPJ) was observed with a strong negative correlation (Spearman's rank correlation coefficient $\rho = -0.87$; $N = 19$; $p = 1.9 \times 10^{-4}$ Bonferroni corrected for 120 regions) between the PRAQ-R2 scores at gwk 24 and the infant HbT responses to sad speech (Fig. 2c; Table 2). Spearman's rank correlation coefficient for the response to sad speech in the TPJ cluster vs. PRAQ-R2 at gwk 24 ($\rho = -0.87$; $N = 18$) was statistically significantly greater than for gwk 34 ($\rho = -0.42$; $N = 18$); $p = 0.0091$ from permutation test. Neither maternal pre- or postnatal general anxiety or depression symptoms, nor the gestational age at birth was statistically significant as confound factors together with the main regressor (PRAQ-R2 at gwk 24) in the multiple regression analysis (as presented in the Supplement).

4. Discussion

The present study investigated the correlation between maternal pregnancy-specific anxiety symptom scores collected at gestational weeks 24 and 34 and infant hemodynamic responses to emotional speech stimuli in the left hemisphere at two months of age recorded using diffuse optical tomography (DOT). We found that at gestational week 24, PRAQ-R2 scores correlated negatively with total hemoglobin responses to sad speech in areas inferior and superior to the left temporoparietal junction (TPJ; MTG = Middle Temporal Gyrus, ITG = Inferior Temporal Gyrus, FFG = Fusiform Gyrus, STG = Superior Temporal Gyrus, SMG = Supramarginal Gyrus) (Fig. 2; Table 2).

Our results are in line with the developmental origins of behavior, health and disease (DOHaD) hypothesis (Barker, 1998) which proposes that intrauterine and maternal conditions during pregnancy may affect the neurodevelopmental pathways of the fetus and child (Van den Bergh, 2011; Gluckman et al., 2009; Räikkönen et al., 2011). Previous research suggests a connection between maternal prenatal anxiety (psychological distress, life event stress and objective exposure) and neurocognitive outcomes of the infants (Mulder et al., 2002; Van den Bergh et al., 2005b; Van den Heuvel et al., 2015; Van den Bergh et al., 2017). Otte et al. (2015) studied ERP responses to happy and fearful face/voice pairs in 9-month-old infants and reported larger P350

Table 1
Descriptive statistics of the mother-infant dyad sample ($N = 19$). Instead of median and range, for the education level we indicate frequencies and percentages (L1 = lower or middle level education (up to 12 years of education), L2 = vocational/applied university degree (up to 15 years of education), L3 = university degree (more than 15 years of education)).

Subject	Characteristic	Median	Range
Infants ($N = 19$)	Age at measurement calculated from the birthdate (days)	53	43 - 71
	Head circumference at birth (cm)	38.5	33.0 – 41.9
	Birth weight (g)	3500	2525 – 4175
	Birth height (cm)	51	47 – 54
	Gestational age at delivery (weeks)	39.7	37.3 – 41.9
Mothers ($N = 19$)	Maternal age at measurement (years)	32.1	21.4 – 37.3
	Maternal Body Mass Index, kg/m^2 (BMI)	22.5	19.5 – 35.4
	PRAQ-R2 total score at gestational week 24$$	20.0	10.0 – 45.0
	PRAQ-R2 total score at gestational week 34 ($N = 18$)	20.0 Level	13.0 – 40.0 Frequency (%)
	Education level (3-step scale)	L1	6 (32%)
		L2	2 (11%)
		L3	11 (58%)

amplitudes in response to fearful vocalizations and smaller P350 amplitudes in response to happy vocalizations when the infants had been exposed to higher levels of anxiety (maternal state anxiety score measured before gwk 15). As TPJ has been involved in the "theory of mind", or reasoning about another person's mental states (Saxe and Kanwisher, 2003), and the superior temporal sulcus (STS) has been proposed to be involved in both speech and social perception (Frith and Frith, 2007; Blakemore, 2008; Redcay, 2008), reduced processing of sad speech in these areas could reflect the influence of maternal pregnancy-specific anxiety on the infants' social cognitive processes although the functional relevance of these observations remains to be investigated.

Comparison with earlier studies using pregnancy-related anxiety questionnaires when measuring maternal prenatal stress prior to infant neuroimaging is precluded by the scarcity of such studies. However, our findings are in line with recent studies that have reported the association of maternal generalized anxiety with behavioral and emotional outcomes in children. For example, it has been found that maternal generalized anxiety (assessed using the anxiety items from the Crown-Crisp index) is a predictor of behavioral problems (inattentivity/hyperactivity) in 4-year-olds and behavioral and/or emotional problems in 7-year-olds (O'Connor et al., 2002a, 2002b). Kataja et al. found that maternal pre- but not postnatal general anxiety symptoms were associated with higher threat bias in infants (as reflected by the probability of disengagement from fearful faces in an eye movement tracking task). Furthermore, the relationship between maternal generalized anxiety symptoms in early pregnancy (gestational week 14) and higher threat bias in infants remained significant even after controlling for maternal postnatal symptoms (at 6 months post-partum) (Kataja et al., 2019). Huizink et al. found that maternal anxiety at 15–17 weeks and pregnancy-specific anxiety at 27–28 weeks were associated with infant attention-regulation problems at 3 months and 8 months (Huizink et al., 2002, 2003). Van den Bergh et al. found that maternal state anxiety at 12–22 weeks of gestation was a significant predictor of anxiety and externalizing problems in 8- to 9-year-old children and cognitive functioning at age 14–15, whereas anxiety at 32–40 weeks was not (Van den Bergh and Marconen, 2004; Van den Bergh et al., 2005a). Taken together with our results, maternal anxiety and maternal pregnancy-related anxiety at different time points during pregnancy might be variably associated with behavioral and emotional outcomes in children; however, more research is needed to form conclusive evidence. To link our observations on infant brain responses to emotional speech and socio-emotional development of children, further research is needed to make any conclusions about the relationship between the TPJ sensitivity to sad stimuli and later behavioral outcomes in children.

Animal studies have suggested that permanent alterations in hypothalamic-pituitary-axis (HPA axis) can occur in the offspring, if they are exposed prenatally to maternal stress (Lucas, 1991; Weinstock et al., 1992; Clarke et al., 1994; Henry et al., 1994; Barbazanges et al., 1996; Maccari et al., 2003; Grant et al., 2009). Maternal prenatal State and Trait anxiety increases the fetal exposure to cortisol by down-regulating the enzyme called placental 11β-hydroxysteroid dehydrogenase type-2 (O'Donnell et al., 2012). In addition, there might be genetic factors that mediate the effects of maternal anxiety on the infant responses to emotional speech. The precise mechanism by which maternal prenatal anxiety would affect fetal neural programming in humans is not yet fully understood (Van den Bergh et al., 2005b; Buss et al., 2011) and warrants more research.

Due to the neurovascular coupling, increased synaptic activity leads to an increase in arteriolar and possibly capillary diameter and increased cerebral blood volume (CBV), flow (CBF), and HbT (Hillman et al., 2007; Mishra et al., 2016). Since arteriolar blood has a higher oxygen saturation than venous blood, the tissue oxygen saturation increases in the affected region, leading to increased HbO_2 and decreased HbR, which is sometimes referred to as the typical or canonical hemodynamic response (Issard and Gervain, 2018). Responses which show the opposite polarity (either negative HbO_2, HbT and/or positive HbR changes) are called inverted responses (Issard and Gervain, 2018). In the present study, we observed negative HbT

Table 2
Regions with statistically significant correlations between pregnancy-related anxiety (PRAQ-R2) and infant response to emotional speech. N_{vox} = number of voxels in the cluster, Gwk = gestational week. ρ = Spearman's rank correlation coefficient. Multiple comparison performed to achieve the corrected p-value using the Bonferroni method with 120 regions. * = statistically significant with corrected p-value < 0.05 using a correction factor $N_{MC} = 120$. ** = Statistically significant with Bonferroni correction for 120 regions, 4 emotions and 2 stress scores. MTG = Middle Temporal Gyrus, ITG = Inferior Temporal Gyrus, FFG = Fusiform Gyrus, STG = Superior Temporal Gyrus, SMG = Supramarginal Gyrus. The infant MNI coordinates were calculated from the infant template by Shi et al., 2011.

Region	N_{vox}	Emotion	Gwk	Coordinates	ρ	p-value(uncorrected)	p-value(corrected)
Temporoparietal junction (MTG-L, ITG-L, FFG-L, STG-L, SMG-L)	1928	Sad	24	Infant (−31, −31,4) Adult (−45, −37,21)	−0.87**	1.6×10^{-6}	1.9×10^{-4}**

responses to sad speech in the TPJ cluster in the infants of mothers who reported higher levels of pregnancy-related anxiety and positive HbT responses in the infants of mothers who reported lower levels of pregnancy-specific anxiety during pregnancy. Responses to auditory stimuli in the temporal and parietal cortices with both positive and negative sign have been reported in adults (while awake) using NIRS (Bauernfeind et al., 2018), and reduced or negative BOLD responses in the temporal cortex are found in adult subjects during sleep (Czisch et al., 2002, 2004). Although we were not able to determine the infant's the sleep stage in the present study, most of the stimuli accepted into averaging were likely presented during sleep. The infants are more active during awake periods, potentially leading to frequent artifacts and epoch rejection (Jönsson et al., 2018). It is possible that sleep stage is a contributing factor to reduced or negative responses to auditory stimuli. The variability in the hemodynamic response in infant fNIRS measurements is discussed, e.g., in Issard and Gervain (2018). In the temporal cortex, both inverted and typical responses to auditory stimuli are reported in newborn infants between subjects using the same stimulus conditions as well as within participants between different stimulus conditions (Issard and Gervain, 2018). In adults, both typical and inverted responses to auditory stimuli are also reported (Bauernfeind et al., 2018). The inverted response may be a sign of *deactivation*, in which case the neuronal activity may be reduced due to inhibitory inputs, a reduction of the resting state activity (Raichle and Mintun, 2006; Hayes and Huxtable, 2012), or due to habituation when the stimulus is repeated or several stimuli are presented in a quick succession (Kusherenko et al., 2013; Guiraud et al., 2011). Deactivation may occur when the stimulus is regarded irrelevant (Grossmann et al., 2010). Another possible explanation for negative responses is *blood stealing*, i.e., activation in a different area may lead to reduced blood flow to the surrounding areas without central control due to the finite overall capacity of the cardiovascular system (Tomasi et al., 2006). Due to the limited spatial resolution of DOT, it is possible that regions with negative HbT responses may affect the reconstructed values also in adjacent regions with positive HbT responses, as both polarities of responses are seen in temporal and parietal cortex (Issard and Gervain, 2018; Bauernfeind et al., 2018). If a region of the brain is activated to a stimulus in a PRA-modulated way, adjacent regions (which may be deactivated or show otherwise negative responses) may pull down the reconstructed values leading to a range of negative to positive values instead of a range from zero to positive values because the reconstruction is not able to resolve such fine details between regions. Furthermore, differences across subjects in the spatial location of activated areas may contribute to the loss of fine detail when investigating group-level phenomena such as the correlation analysis in the present study. If we assume that more positive HbT responses indicate greater activity and more negative responses reduced activity, then the result suggests that the healthy mothers' infants have greater activation in the TPJ due to the processing of sad speech and the infants born to anxious mothers have suppressed processing of sad speech in this area. Comparison of electrophysiological and hemodynamic responses using the same subjects and stimulus protocols may also be help understand the meaning of positive and negative HbT responses in general, and specifically, if the infant responses differ from those of adult subjects.

4.1. Limitations

Although the questionnaire data were collected at specific points of gestation, we cannot be certain about the exact duration of pregnancy-related anxiety experienced by the mothers in our study. Despite the fact that the effects of maternal generalized anxiety cannot be completely disentangled from pregnancy-related anxiety, our study specifically illustrates the association between pregnancy-related anxiety and infant neural hemodynamic responses to emotional speech. A limitation of this study was that we did not control for anxiety symptoms in fathers during pregnancy. Maternal pre- and postnatal generalized anxiety and depression were not found to be significant co-explanatory factors in a linear multiple regression analysis (see the Supplement for details). Although individual subject specific MRI's of each subject would have made modeling light propagation and visualization of results more precise, it was not realistic to require each subject to undergo both studies in quick succession. The use of a newborn atlas based on averaging a large number of subjects was rejected because of the large differences in head shapes between newborns and infants of two months of age. Because of the diffusive nature of light propagation, and the solution of the inverse problem, perfect localization of the resulting changes is not possible and the results should be viewed as estimates based on the information available. Lastly, the imaging method used in this study is not sensitive to the deepest parts of the brain, the probe was positioned mainly over temporal and parietal regions, and a large part of the frontal cortex and the right hemisphere entirely were outside of the FOV. Additional studies are called for to investigate responses in areas of the brain not covered in this study. A larger data set would have been desirable to provide a more comprehensive analysis of the effects of the different stress factors and to better represent a larger population, but this was not possible in the current study. The effect found was, however, highly statistically significant within such a large volume of the cortex that it should be easily reproducible using similar methods. Due to the rejection of over one-half of the recruited subjects, the representativeness of the sample may be questioned. We did not find statistically significant differences in the maternal education, pregnancy-related anxiety, prenatal or postnatal general anxiety, or postnatal depression scores between the successfully measured and rejected subject groups. Prenatal depression scores were slightly higher for the successfully measured than the rejected subject groups (see Supplement for details). The influence of the infant-mother interaction on the measured data was not investigated in this study, which can be considered a limitation. However, coding of the infant-mother interaction events and coupling them with coinciding emotional speech stimuli would lead to difficulties in obtaining sufficient number of averages for each event to achieve a reliable analysis. The study population included a relatively large proportion of highly educated mothers; 58% of the mothers had university degrees.

5. Conclusion

In this pilot study, we looked into the relationship between maternal pregnancy-related anxiety (PRA) in mid- and late pregnancy and infant responses to emotional speech at two months of age. We discovered that in areas around the temporoparietal junction (TPJ), the infant response to sad speech correlates negatively with maternal PRA in mid-pregnancy and that this correlation is stronger in mid- than late pregnancy. The TPJ receives inputs from the auditory cortex as well as the limbic system, thus it is logical that if exposure to PRA alters the development of the limbic system in the fetus, this would lead to a correlation between PRA and responses to emotional speech in this area of the child's brain. In infants, the observed large inter-subject variability between responses to stimuli is sometimes interpreted as a sign of the immaturity of the brain, or a result of flaws in the research or neuroimaging methodology. The results in this study suggest that maternal PRA in mid-pregnancy may explain a large part of the inter-subject variability in infant responses to affective stimuli. The stronger effect observed for PRA in mid- rather than late pregnancy may indicate a biochemical rather than sensory mechanism as more likely. Future studies of maternal PRA at different phases of gestation and the child's neurodevelopmental outcomes with a larger number of subjects are needed to understand the implications of exposure to maternal pregnancy-related anxiety on the child's cognitive and emotional development. As instrumentation, modeling and analysis techniques for the neuroimaging of children evolve, more detailed information of the child's brain development can be obtained. Finally, the long-term socio-

emotional significance of the observed variation in emotional speech processing during infancy needs to be further investigated by longitudinal studies.

Author statement

Contributors

Authors AM, SS, HK, LK, MH, KK and IN designed the study; SS, KK and IN performed the optical imaging experiments. AM, IN, SS, KK, JT, and PH analysed the data. Authors AM and IN wrote the manuscript and all authors contributed to the final form of the paper.

Role of the funding source

This work was supported by the Academy of Finland [grant numbers 269282 (to IN); 273451 and 303937 (to IN, KK); 134950 (to HK); 253270 (to HK)], Jane and Aatos Erkko Foundation (to HK), Signe and Ane Gyllenberg Foundation (to HK, LK), State Research Grant (EVO) (to HK, LK, JJT), Yrjö Jahnsson Foundation (LK), the Finnish Society of Sciences and Letters 2012 (to SS), the National Graduate School of Clinical Investigation (VKTK) 2012 (to SS). The funding sources had no involvement in the study design, in the collection, analysis or interpretation of the data, in the writing of the report or the decision to submit the article for publication.

Ethical review

The Ethics Committee of the University of Turku approved the study protocol, and the study was conducted according to the Declaration of Helsinki. Informed written consent was obtained from the parents on behalf of the infants before the measurement.

Declaration of Competing Interest

None.

Acknowledgements

The authors would like to thank Anika Aishani Jha for the illustration in Fig. 1a. IN would like to thank Dr. Johanna Metsomaa for her contribution to the validation of the clustering. We acknowledge the computational resources provided by the Aalto Science-IT project.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.10.047.

References

Arimitsu, T., Uchida-Ota, M., Yagihashi, T., Kojima, S., Watanabe, S., Hokuto, I., Ikeda, K., Takahashi, K., Minagawa-Kawai, Y., 2011. Functional hemispheric specialization in processing phonemic and prosodic auditory changes in neonates. Front. Psychol. 2, 202.

Bachorowski, J., 1999. Vocal expression and perception of emotion. Curr. Dir. Psychol. Sci. 8, 53–57.

Barbazanges, A., Piazza, P.V., Moal, L., Maccari, S., 1996. Maternal glucocorticoid secretion mediates long-term effects of prenatal stress. J. Neurosci. 16, 3943–3949.

Barker, D.J., 1998. In utero programming of chronic disease. Clin. Sci. (Lond.) 95, 115–128.

Bauernfeind, G., Wriessnegger, S.C., Haumann, S., Lenarz, T., 2018. Cortical activation patterns to spatially presented pure tone stimuli with different intensities measured by functional near-infrared spectroscopy. Hum. Brain Mapp. 39, 2710–2724.

Blackmore, E.R., Gustafsson, H., Gilchrist, M., Wyman, C., O'Connor, T.G., 2016. Pregnancy-related anxiety: evidence of distinct clinical significance from a prospective longitudinal study. J. Affect. Disord. 197, 251–258.

Blakemore, S., 2008. The social brain in adolescence. Nature Rev. Neurosci. 9, 267–277.

Blasi, A., Mercure, E., Lloyd-Fox, S., Thomson, A., Brammer, M., Sauter, D., Deeley, Q., Barker, G.J., Renvall, V., Deoni, S., Gasston, D., Williams, S.C.R., Johnson, M.H., Simmons, A., Murphy, D.G.M., 2011. Early specialization for voice and emotion processing in the infant brain. Curr. Biol. 21, 1220–1224.

Buss, C., Davis, E.P., Hobel, C.J., Sandman, C.A., 2011. Maternal pregnancy-specific anxiety is associated with child executive function at 6–9 years age. Stress 14, 665–676.

Buss, C., Davis, E.P., Muftuler, L.T., Head, K., Sandman, C.A., 2010. High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6–9-year-old children. Psychoneuroendocrinology 35, 141–153.

Clarke, A.S., Wittwer, D.J., Abbott, D.H., Schneider, M.L., 1994. Long-term effects of prenatal stress on HPA axis activity in juvenile rhesus monkeys. Dev. Psychobiol. 27, 257–269.

Cope, M., 1991. The Development of a near Infrared Spectroscopy System and Its Application for Non Invasive Monitoring of Cerebral Blood and Tissue Oxygenation in the Newborn infants. PhD Thesis. University College London, London.

Culver, J.P., Siegel, A.M., Franceschini, M.A., Mandeville, J.B., Boas, D.A., 2005. Evidence that cerebral blood volume can provide brain activation maps with better spatial resolution than deoxynated hemoglobin. Neuroimage 27, 947–959.

Czisch, M., Wehrle, R., Kaufmann, C., Wetter, T.C., Holsboer, F., Pollmacher, T., Auer, D.P., 2004. Functional MRI during sleep: BOLD signal decreases and their electrophysiological correlates. Eur. J. Neurosci. 20, 566–574.

Czisch, M., Wetter, T.C., Kaufmann, C., Pollmächer, T., Holsboer, F., Auer, D.P., 2002. Altered processing of acoustic stimuli during sleep: reduced auditory activation and visual deactivation detected by a combined fMRI/EEG study. Neuroimage 16, 251–258.

Davis, E.P., Sandman, C.A., 2010. The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. Child Dev. 81, 131–148.

Davis, E.P., Sandman, C.A., 2012. Prenatal psychobiological predictors of anxiety risk in preadolescent children. Psychoneuroendocrinology 37, 1224–1233.

Fang, Q., Boas, D.A., 2009. Monte Carlo simulation of photon migration in 3D turbid media accelerated by graphics processing units. Opt. Express 17, 20178–20190.

Frith, C.D., Frith, U., 2007. Social cognition in humans. Curr. Biol. 17, 724–732.

Gluckman, P.D., Hanson, M.A., Buklijas, T., 2009. A conceptual framework for the developmental origins of health and disease. J. Dev. Orig. Health Dis. 1, 6–18.

Goodman, S.H., Rouse, M.H., Connell, A.M., Broth, M.R., Hall, C.M., Heyward, D., 2011. Maternal depression and child psychopathology: a meta-analytic review. Clin. Child Fam. Psychol. Rev. 14, 1–27.

Graham, A.M., Fisher, P.A., Pfeifer, J.H., 2013. What sleeping babies hear. Psychol. Sci. 24, 782–789.

Grant, K., McMahon, C., Austin, M., Reilly, N., Leader, L., Ali, S., 2009. Maternal prenatal anxiety, postnatal caregiving and infants' cortisol responses to the still-Face procedure. Dev. Psychobiol. 51, 625–637.

Grossmann, T., Oberecker, R., Koch, S.P., Friederici, A.D., 2010. The developmental origins of voice processing in the human brain. Neuron 65, 852–858.

Harvison, K.W., Molfese, D.L., Woodruff-Borden, J., Weigel, R.A., 2009. Neonatal auditory evoked responses are related to perinatal maternal anxiety. Brain Cogn. 71, 369–374.

Herba, C.M., Glover, V., Ramchandani, P.G., Rondon, M.B., 2016. Maternal depression and mental health in early childhood: an examination of underlying mechanisms in low-income and middle-income countries. The Lancet Psychiatry 3, 983–992.

Heiskala, J., Hiltunen, P., Nissilä, I., 2009. Significance of background optical properties, time-resolved information and optode arrangement in diffuse optical imaging of term neonates. Phys. Med. Biol. 54, 535.

Henry, C., Kabbaj, M., Simon, H., Le Moal, M., Maccari, S., 1994. Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. J. Neuroendocrinol. 6, 341–345.

Hillman, E.M.C., Devor, A., Bouchard, M., Dunn, A.K., Krauss, G.W., Skoch, J., Bacskai, B.J., Dale, A.M., Boas, D.A., 2007. Depth-resolved optical imaging and microscopy of vascular compartment dynamics during somatosensory stimulation. Neuroimage 35, 89–104.

Huizink, A.C., Delforterie, M.J., Scheinin, N.M., Tolvanen, M., Karlsson, L., Karlsson, H., 2016. Adaption of pregnancy anxiety questionnaire–revised for all pregnant women regardless of parity: PRAQ-R2. Archive Women's Mental Health 19, 125–132.

Huizink, A.C., Medina, P.G., Mulder, E.J., Visser, G.H., Buitelaar, J.K., 2002. Psychological measures of prenatal stress as predictors of infant temperament. J. Am. Acad. Child Adolesc. Psychiatry 41, 1078–1085.

Huizink, A.C., Medina, P.G., Mulder, E.J., Visser, G.H., Buitelaar, J.K., 2003. Stress during pregnancy is associated with developmental outcome in infancy. J. Child Psychol. Psychiatry 44, 810–818.

Huizink, A.C., Mulder, E.J.H., Robles de Medina, P.G., Visser, G.H.A., Buitelaar, J.K., 2004. Early Hum. Dev. 79, 81–91.

Hunter, S.K., Mendoza, J.H., D'Anna, K., Zerbe, G.O., McCarthy, L., Hoffman, C., Freedman, R., Ross, R.G., 2012. Antidepressants may mitigate the effects of prenatal maternal anxiety on infant auditory sensory gating. Am. J. Psychiatry 169, 616–624.

Issard, C., Gervain, J., 2018. Variability of the hemodynamic response in infants: influence of experimental design and stimulus complexity. Dev. Cogn. Neurosci. https://doi.org/10.1016/j.dcn.2018.01.009.

Johar, S., 2015. Psychology of voice. Emotion Affect Personal. Speech SpringerBriefs Electric. Comp. Eng. 9–15.

Jönsson, E.H., Kotilahti, K., Heiskala, J., Wasling, H.B., Olausson, H., Croy, I., Mustaniemi, H., Hiltunen, P., Tuulari, J.J., Scheinin, N.M., Karlsson, L., Karlsson, H., Nissilä, I., 2018. Affective and non-affective touch evoke differential brain responses in 2-month-old infants. Neuroimage 169, 162–171.

Juslin, P.N., Laukka, P., 2003. Communication of emotions in vocal expression and music performance: different channels, same code? Psychol. Bull. 129, 770–814.

Karlsson, L., Tolvanen, M., Scheinin, N.M., Uusitupa, H.M., Korja, R., Ekholm, E., Tuulari, J.J., Pajulo, M., Huotilainen, M., Paunio, T., Karlsson, H., 2018. Cohort profile: the

FinnBrain birth cohort study (FinnBrain). Int. J. Epidemiol. 47, 15–16.
Kataja, E., Karlsson, L., Parsons, C.E., Pelto, J., Pesonen, H., Häikiö, T., Hyönä, J., Nolvi, S., Korja, R., Karlsson, H., 2019. Maternal pre- and postnatal anxiety symptoms and infant attention disengagement from emotional faces. J. Affect. Disord. 243, 280–289.
Korja, R., Nolvi, S., Grant, K.A., McMahon, C., 2017. The relations between maternal prenatal anxiety or stress and child's early negative reactivity or self-regulation: a systematic review. Child Psychiatry Hum. Dev. 48, 851–869.
Kotilahti, K., Nissilä, I., Huotilainen, M., Mäkelä, R., Gavrielides, N., Noponen, T., Björkman, P., Fellman, V., Katila, T., 2005. Bilateral hemodynamic responses to auditory stimulation in newborn infants. Neuroreport 16, 1373–1377.
Kotilahti, K., Nissilä, I., Näsi, T., Lipiäinen, L., Noponen, T., Meriläinen, P., Huotilainen, M., Fellman, V., 2010. Hemodynamic responses to speech and music in newborn infants. Hum. Brain Mapp. 31, 595–603.
Lee, C.W., Cooper, R.J., Austin, T., 2017. Diffuse optical tomography to investigate the newborn brain. Pediatr. Res. 82, 376–386.
Lucas, A., 1991. Programming by early nutrition in man. Ciba Found Symp. 156, 38–50.
Maccari, S., Darnaudery, M., Morley-Fletcher, S., Zuena, A.R., Cinque, C., Van Reeth, O., 2003. Prenatal stress and long-term consequences: implications of glucocorticoid hormones. Neurosci. Biobehav. Rev. 27, 119–127.
Maria, A., Shekhar, S., Nissilä, I., Kotilahti, K., Huotilainen, M., Karlsson, L., Karlsson, H., Tuulari, J.J., 2018. Emotional processing in the first 2 years of life: a review of near-infrared spectroscopy studies. J. Neuroimag. 28, 441–454.
Martin, R.P., Noyes, J., Wisenbaker, J., Huttunen, M.O., 1999. Prediction of early childhood negative emotionality and inhibition from maternal distress during pregnancy. Merrill Palmer Q. 45, 370–391.
Mennes, M., Bergh, B.V., Lagae, L., Stiers, P., 2009. Developmental brain alterations in 17 year old boys are related to antenatal maternal anxiety. Clinic. Neurophysiol. 120, 1116–1122.
Mennes, M., Stiers, P., Lagae, L., Vandenbergh, B., 2006. Long-term cognitive sequel of antenatal maternal anxiety: involvement of the orbitofrontal cortex. Neurosci. Biobehav. Rev. 30, 1078–1086.
Mishra, A., Reynolds, J.P., Chen, Y., Gourine, A.V., Rusakov, D.A., Attwell, D., 2016. Astrocytes mediate neurovascular signalling to capillary pericytes but not to arteriles. Nat. Neurosci. 19, 1619–1627.
Mulder, E., Medina, P.R., Huizink, A., Bergh, B.V., Buitelaar, J., Visser, G., 2002. Prenatal maternal stress: effects on pregnancy and the (unborn) child. Early Hum. Dev. 70, 3–14.
Naoi, N., Fuchino, Y., Shibata, M., Niwa, F., Kawai, M., Konishi, Y., Okanoya, K., Myowa, Yamakoshi, M., 2013. Decreased right temporal activation and increased inter-hemispheric connectivity in response to speech in preterm infants at Term-Equivalent Age. Front. Psychol. 4, 94.
Naoi, N., Minagawa-Kawai, Y., Kobayashi, A., Takeuchi, K., Nakamura, K., Yamamoto, J., Kojima, S., 2012. Cerebral responses to infant-directed speech and the effect of talker familiarity. Neuroimage 59, 1735–1744.
Näsi, T., Mäki, H., Hiltunen, P., Heiskala, J., Nissilä, I., Kotilahti, K., Ilmoniemi, R.J., 2013. Effect of task-related extracerebral circulation on diffuse optical tomography: experimental data and simulations on the forehead. Biomed. Opt. Express. 4, 412–426.
Nissilä, I., Kotilahti, K., Fallström, K., Katila, T., 2002. Instrumentation for the accurate measurement of phase and amplitude in optical tomography. Rev. Sci. Instru. 73, 3306–3312.
Nissilä, I., Noponen, T., Kotilahti, K., Katila, T., Lipiäinen, L., Tarvainen, T., Schweiger, M., Arridge, S., 2005. Instrumentation and calibration methods for the multichannel measurement of phase and amplitude in optical tomography. Rev. Sci. Instru. 76, 044302.
Nolvi, S., Karlsson, L., Bridgett, D.J., Korja, R., Huizink, A.C., Kataja, E., Karlsson, H., 2016. Maternal prenatal stress and infant emotional reactivity six months post-partum. J. Affect. Disord. 199, 163–170.
O'Connor, T.G., Heron, J., Glover, V., 2002 aAa. Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. J. Am. Acad. Child Adolesc. Psychiatry 41, 1470–1477.
O'Connor, T.G., Heron, J., Golding, J., Beveridge, M., Glover, V., 2002 bAb. Maternal antenatal anxiety and children's behavioral/emotional problems at 4 years. Br. J. Psychiatry 180, 502–508.
O'Connor, T.G., Heron, J., Golding, J., Glover, V., 2003. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. J. Child Psychol. Psychiatry 44, 1025–1036.
O'Donnell, K.J., Jensen, A.B., Freeman, L., Khalife, N., O'Connor, T.G., Glover, V., 2012. Maternal prenatal anxiety and downregulation of placental 11β-HSD2. Psychoneuroendocrinology 37, 818–826.
Otte, R., Donkers, F., Braeken, M., Bergh, B.V., 2015. Multimodal processing of emotional information in 9-month-old infants II: prenatal exposure to maternal anxiety. Brain Cogn. 95, 107–117.
Peña, M., Maki, A., Kovacic, D., Dehaene-Lambertz, G., Koizumi, H., Bouquet, F., Mehler, J., 2003. Sounds and silence: an optical topography study of language recognition at birth. Proc. Natl. Acad. Sci. U. S. A. 100, 11702–11705.
Räikkönen, K., Seckl, J.R., Pesonen, A., Simons, A., Van den Bergh, B.R.H., 2011. Stress, glucocorticoids and liquorice in human pregnancy: programmers of the offspring brain. Stress 14, 590–603.
Reck, C., Zimmer, K., Dubber, S., Zipser, B., Schlehe, B., Gawlik, S., 2013. The influence of general anxiety and childbirth-specific anxiety on birth outcome. Archive Women's Mental Health 16, 363–369.
Redcay, E., 2008. The superior temporal sulcus performs a common function for social and speech perception: implications for the emergence of autism. Neurosci. Biobehav. Rev. 32, 123–142.
Saito, Y., Aoyama, S., Kondo, T., Fukumoto, R., Konishi, N., Nakamura, K., Kobayashi, M., Toshima, T., 2007. Frontal cerebral blood flow change associated with infant-directed speech. Arch. Dis. Child Fetal Neonatal Ed. 92, F113–F116.
Saito, Y., Fukuhara, R., Aoyama, S., Toshima, T., 2009. Frontal brain activation in premature infants' response to auditory stimuli in neonatal intensive care unit. Early Hum. Dev. 85, 471–474.
Saxe, R., Kanwisher, N., 2003. People thinking about thinking people: the role of the temporoparietal junction in "theory of mind" Neuroimage 19, 1835–1842.
Scherer, K.R., 1986. Vocal affect expression: a review and a model for future research. Psychol. Bull. 99, 143–165.
Scherer, K.R., 1995. Expression of emotion in voice and music. J Voice 9, 235–248.
Schetter, C.D., Tanner, L., 2012. Anxiety, depression and stress in pregnancy. Curr. Opin. Psychiatry 25, 141–148.
Shekhar, S., Maria, A., Kotilahti, K., Huotilainen, M., Heiskala, J., Tuulari, J.J., Hirvi, P., Karlsson, L., Karlsson, H., Nissilä, I., 2019. Hemodynamic responses to emotional speech in two-month-old infants imaged using diffuse optical tomography. Sci. Rep. 9, 4745.
Shi, F., Yap, P., Wu, G., Jia, H., Gilmore, J.H., Lin, W., Shen, D., 2011. Infant brain atlases from neonates to 1- and 2-Year-Olds. PLoS ONE 6, e18746.
Telkemeyer, S., Rossi, S., Koch, S.P., Nierhaus, T., Steinbrink, J., Poeppel, D., Obrig, H., Wartenburger, I., 2009. Sensitivity of newborn auditory cortex to the temporal structure of sounds. J. Neurosci. 29, 14726–14733.
Van den Bergh, B.R.H., 2011. Developmental programming of early brain and behaviour development and mental health: a conceptual framework. Dev. Med. Child Neurol. 53, 19–23.
Van den Bergh, B.R.H., Marcoen, A., 2004. High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-Year-Olds. Child Dev. 75, 1085–1097.
Van den Bergh, B.R.H., Mennes, M., Oosterlaan, J., Stevens, V., Stiers, P., Marcoen, A., Lagae, L., 2005Aa. High antenatal maternal anxiety is related to impulsivity during performance on cognitive tasks in 14- and 15-year-olds. Neurosci. Biobehav. Rev. 29, 259–269.
Van den Bergh, B.R.H., Mulder, E.J., Mennes, M., Glover, V., 2005Ab. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. Neurosci. Biobehav. Rev. 29, 237–258.
Van den Bergh, B.R.H., van den Heuvel, M.I., Lahti, M., Braeken, M., de Rooij, S.R., Entringer, S., Hoyer, D., Roseboom, T., Räikkönen, K., King, S., Schwab, M., 2017. Prenatal developmental origins of behavior and mental health: the influence of maternal stress in pregnancy. Neurosci. Biobehav. Rev. 30734–30735 S0149-7634.
Van den Heuvel, M.I., Donkers, F.C.L., Winkler, I., Otte, R.A., Van den Bergh, B.R.H., 2014. Maternal mindfulness and anxiety during pregnancy affect infants' neural responses to sounds. Soc. Cogn. Affect. Neurosci. 10, 453–460.
Wachs, T.D., Black, M.M., Engle, P.L., 2009. Maternal depression: a global threat to children's health, development, and behavior and to human rights. Child Dev. Perspect. 3, 51–59.
Weinstock, M., Matlina, E., Maor, G.I., Rosen, H., McEwen, B.S., 1992. Prenatal stress selectively alters the reactivity of the hypothalamic-pituitary adrenal system in the female rat. Brain Res. 595, 195–200.
Zeff, B.W., White, B.R., Dehghani, H., Schlaggar, B.L., Culver, J.P., 2007. Retinotopic mapping of adult human visual cortex with high-density diffuse optical tomography. Proc. Natl. Acad. Sci. U. S. A. 104, 12169–12174.
Zhang, D., Zhou, Y., Hou, X., Cui, Y., Zhou, C., 2017. Discrimination of emotional prosodies in human neonates: a pilot fNIRS study. Neurosci. Lett. 658, 62–66.